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MORAXELLA CATARRHALIS BASB034 POLYPEPTIDES AND USES THEREOF**FIELD OF THE INVENTION**

This invention relates to polynucleotides, (herein referred to as "BASB034 polynucleotide(s)"), polypeptides encoded by them (referred to herein as "BASB034" or "BASB034 polypeptide(s)"), recombinant materials and methods for their production. In another aspect, the invention relates to methods for using such polypeptides and polynucleotides, including vaccines against bacterial infections. In a further aspect, the invention relates to diagnostic assays for detecting infection of certain pathogens.

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BACKGROUND OF THE INVENTION

Moraxella catarrhalis (also named *Branhamella catarrhalis*) is a Gram negative bacteria frequently isolated from the human upper respiratory tract. It is responsible for several pathologies the main ones being otitis media in infants and children, and pneumonia in elderlies. It is also responsible of sinusitis, nosocomial infections and less frequently of invasive diseases.

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Otitis media is an important childhood disease both by the number of cases and its potential sequelae. More than 3.5 millions cases are recorded every year in the United States, and it is estimated that 80 % of the children have experienced at least one episode of otitis before reaching the age of 3 (Klein, JO (1994) Clin.Inf.Dis 19:823). Left untreated, or becoming chronic, this disease may lead to hearing losses that could be temporary (in the case of fluid accumulation in the middle ear) or permanent (if the auditive nerve is damaged). In infants, such hearing losses may be responsible for a delayed speech learning.

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Three bacterial species are primarily isolated from the middle ear of children with otitis media: *Streptococcus pneumoniae*, non typeable *Haemophilus influenza* (NTHi) and *M. catarrhalis*. They are present in 60 to 90 % of the cases. A review of recent studies shows that *S. pneumoniae* and NTHi represent both about 30 %. and *M. catarrhalis* about 15 % of

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the otitis media cases (Murphy, TF (1996) Microbiol.Rev. 60:267). Other bacteria could be isolated from the middle ear (*H. influenza* type B, *S. pyogenes* etc) but at a much lower frequency (2 % of the cases or less).

- 5 Epidemiological data indicate that, for the pathogens found in the middle ear, the colonization of the upper respiratory tract is an absolute prerequisite for the development of an otitis; other are however also required to lead to the disease (Dickinson, DP et al. (1988) J. Infect.Dis. 158:205, Faden, HL et al. (1991) Ann.Otorhinol.Laryngol. 100:612). These are important to trigger the migration of the bacteria into the middle ear via the Eustachian
- 10 tubes, followed by the initiation of an inflammatory process. These factors are unknown todate. It has been postulated that a transient anomaly of the immune system following a viral infection, for example, could cause an inability to control the colonization of the respiratory tract (Faden, HL et al (1994) J. Infect.Dis. 169:1312). An alternative explanation is that the exposure to environmental factors allow a more important colonization of some
- 15 children, who subsequently become susceptible to the development of otitis media because of the sustained presence of middle ear pathogens (Murphy, TF (1996) Microbiol.Rev. 60:267).

- The immune response to *M. catarrhalis* is poorly characterized. The analysis of strains
- 20 isolated sequentially from the nasopharynx of babies followed from 0 to 2 years of age, indicates that they get and eliminate frequently new strains. This indicates that an efficacious immune response against this bacteria is mounted by the colonized children (Faden, HL et al (1994) J. Infect.Dis. 169:1312).

- 25 In most adults tested, bactericidal antibodies have been identified (Chapman, AJ et al. (1985) J. Infect.Dis. 151:878). Strains of *M. catarrhalis* present variations in their capacity to resist serum bactericidal activity: in general, isolates from diseased individuals are more resistant than those who are simply colonized (Hol, C et al. (1993) Lancet 341:1281. Jordan. KL et al. (1990) Am.J.Med. 88 (suppl. 5A):28S). Serum resistance could therefore be

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considered as a virulence factor of the bacteria. An opsonizing activity has been observed in the sera of children recovering from otitis media.

The antigens targetted by these different immune responses in humans have not been identified, with the exception of OMP B1, a 84 kDa protein which expression is regulated by iron, and that is recognized by the sera of patients with pneumonia (Sethi, S, et al. (1995) Infect.Immun. 63:1516), and of UspA1 and UspA2 (Chen D. et al.(1999), Infect.Immun. 67:1310).

A few other membrane proteins present on the surface of *M. catarrhalis* have been characterized using biochemical method, or for their potential implication in the induction of a protective immunity (for review, see Murphy, TF (1996) Microbiol.Rev. 60:267). In a mouse pneumonia model, the presence of antibodies raised against some of them (UspA, CopB) favors a faster clearance of the pulmonary infection. Another polypeptide (OMP CD) is highly conserved among *M. catarrhalis* strains, and presents homologies with a porin of *Pseudomonas aeruginosa*, which has been demonstrated efficacious against this bacterium in animal models.

The frequency of *Moraxella catarrhalis* infections has risen dramatically in the past few decades. This has been attributed to the emergence of multiply antibiotic resistant strains and an increasing population of people with weakened immune systems. It is no longer uncommon to isolate *Moraxella catarrhalis* strains that are resistant to some or all of the standard antibiotics. This phenomenon has created an unmet medical need and demand for new anti-microbial agents, vaccines, drug screening methods, and diagnostic tests for this organism.

SUMMARY OF THE INVENTION